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ANNUAL ADDRESS.

MODES OF INFECTION.

BY WILLIAM H. WELCH, M. D.,
Professor of Pathology, Johns Hopkins University, Baltimore.

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Mr. President and Gentlemen, Fellow-members of the Medico-Chirurgical Society:

When honored by the invitation to deliver the Annual Address before this Society, it seemed to me appropriate to select a subject relating to that department of medicine in which the most important discoveries have been made in recent times. The far-reaching advances in our knowledge of the causation of infectious diseases have opened up new fields of view in so many and in so various directions, that I have been somewhat in doubt as to what phase of the subject it would be most profitable for us to consider on the present occasion.

The time has gone by when much profit is to be derived from the discussion of that very general and hackneyed theme, the germ theory of disease; for the doctrine thus expressed is no longer a theory, and there is, doubtless, no one competent to form an opinion on the subject who does not believe that certain infectious diseases are caused by micro-organisms, and that it is a logical inference that the other diseases of this class are produced by parasitic organisms—although there may be differences of opinion as to how far this doctrine has been proven for individual diseases.

I have thought that it might be of interest to pass in review certain fundamental ideas concerning infectious diseases, and to note how far these ideas have been modified or expanded by recent discoveries.

Many of these ideas are by no means of recent origin, for from the earliest times onward much attention has been devoted to the investigation of epidemic diseases, and particularly of their causation. The conceptions of contagium and of miasm are almost as

old as the history of medicine itself. Ancient writers have recorded their belief in the existence of infected localities, and in the conveyance of epidemic diseases by means of the drinking water and of the air. Individual predisposition to infection, as well as predisposition according to time and to place, are not modern ideas, as is shown by such historical terms as *genius epidemicus, constitutio pestilens.* The science of epidemiology is much older than that of bacteriology, and has taught us much concerning the causation and development of infectious diseases.

The question arises: Has our knowledge concerning the origin and spread of infectious diseases been widened and has it become more exact since the discovery of the living contagium of many of these diseases? While granting the vast scientific importance of this discovery, it is in itself only the confirmation of the faith of far-seeing minds of past generations. The mere demonstration of that which was previously a reasonable supposition does not offer a new point of view.

It is proper for us to inquire whether the investigation of the micro-organisms causing infectious diseases, and the study of the characteristics and life histories of these parasites, of the media and conditions of their growth and of the means of their destruction, have added materially to the knowledge which was already afforded us by the epidemiological study of these diseases. Have we thereby gained a clearer conception of such terms as miasm, contagium, and miasmatic contagium? Have we a deeper insight into the conditions under which a virus is transmitted from an infected to a healthy person, and of the conditions of infection through the air, the drinking water and other media? Can we form any more definite ideas of what is meant by individual predisposition to an infectious disease and by such terms as predisposition in time and in place?

Even if we were obliged to answer all of these questions in the negative, not one particle would be detracted from the importance of further pursuit of bacteriological studies, for experience has shown that nothing is more short-sighted than to estimate the value of scientific discoveries according to their immediate practical utility. And, moreover, the questions which I have raised relate to only a few out of many practical aspects of these studies; but if, as I believe to be true, it can be shown that light has been shed upon some of the most interesting and obscure problems concerning infectious diseases, by the studies of the living organisms causing these diseases, then it

is apparent that the results of these studies are of more immediate interest and of interest to a much wider circle than would otherwise be the case.

Our knowledge in the directions indicated is but fragmentary. The title "Modes of Infection" under which I wish to gather together some of these fragments has been selected as a convenient one to cover most of the thoughts which I desire to present to you. The intention, however, is not to consider exhaustively all possible modes of infection, but chiefly to dwell upon such points relating to the causation of infectious diseases as have been most illuminated by recent investigations, particularly in bacteriology.

There is now tolerable unanimity of opinion as to the meaning attached to the terms infection and infectious diseases. Most recent authorities understand by infection the condition produced by the entrance and multiplication of pathogenic micro-organisms within the body. An infectious disease is one which is caused by the invasion and reproduction within the body of pathogenic micro-organisms. To define an infectious agent as a specific poison capable of indefinite multiplication is only to express obscurely the idea just conveyed, for we know and can conceive of no poison capable of indefinite multiplication except a living organism. The analogies formerly drawn from the fermentation and the putrefaction of organic substances, and still preserved in the designation zymotic diseases, have lost all force as an opposing argument since it has been shown that these processes are produced by living organisms. In the absence of any other probable, I may say even conceivable, hypothesis, to refuse to accept the doctrine of a *contagium vivum* as applicable to all infectious diseases because it has been demonstrated only for certain of these diseases, is about as reasonable as to reject the law *omnis cellula e cellula* because this has not been proven for every cell or every species of cell.

We should be by no means justified to substitute in the foregoing definition of infection instead of pathogenic micro-organisms, bacteria or fissure-fungi. It is true that most of the infectious agents with which we have become acquainted are bacteria, but the malarial parasite is a notable exception to this. There are grounds for believing that the specific organisms of some of the infectious diseases may belong to low forms of animal or vegetable life other than the bacteria. Our means for demonstrating the presence of bacteria are comparatively satisfactory, but this cannot be said of most

of the other protozoa, and it is perhaps in consequence of this imperfection of our methods of investigation that so many infectious diseases have resisted successfully our efforts to discover their efficient causes.

It is gratifying, after so much strife, to be able to record this agreement of opinion as to the definition of infection and of infectious diseases in general. It is customary to classify infectious diseases etiologically into contagious, miasmatic, and miasmatic contagious diseases. As to the significance of these terms, and particularly as to the real nature of the so-called miasmatic contagious diseases, there exists great confusion. As the epithets miasmatic, contagious, and miasmatic contagious meet us upon every hand in our investigations of infectious diseases, as they relate to conceptions which lie at the very foundation of our knowledge of the subject, it is manifestly of the utmost importance that their meaning should, if possible, be rendered clear and precise. I question, however, whether these terms any longer suffice for the classification of infectious diseases, although, as Pettenkofer has said, the ideas contagium and miasm are so bred into our flesh and blood that we would as soon think of parting with them as with one of our limbs even after it had become useless.

Originally the distinction between contagium and miasm was sharply defined. There are two attributes which essentially characterize the ordinary conception of contagium, viz. multiplication within the diseased body, and capability of transmission from the diseased to the healthy body. The latter attribute implies, of course, the elimination of the contagious principle in an active state from the diseased body. On the other hand a miasm is produced outside of the body. According to the belief of many writers it does not multiply within the body, and all agree that it is not eliminated from the body in a condition capable of producing infection. Especial emphasis in framing these distinctions was laid, in the case of a contagious disease, upon the origin of the virus within the body (endogenous), and in the case of a miasmatic disease, outside of the body (exogenous). These ideas concerning contagium and miasm answered well enough for the typically contagious diseases such as syphilis and the exanthematous fevers, and for the typically miasmatic disease, malaria. But confusion began during the middle third of the present century when the origin and spread of Asiatic cholera were carefully studied. It was found impossible to classify this

disease under either of the two existing divisions. It has in common with the contagious diseases the characteristic that persons affected with cholera may convey the disease to localities previously free from it, and may prove the starting points of wide-spread epidemics. Cases sometimes occur of which the only natural interpretation is that they have originated from contagion. On the other hand, in infected localities the disease often develops in those who have never seen a cholera patient, much less come into contact with one, while those in attendance upon such patients as a rule are no more liable to the disease than others living in the same locality. Similar observations were made with reference to typhoid fever.

There arose the contest, not yet ended, between the contagionists who held that these diseases are to be ranked as contagious, and the localists who regarded them as miasmatic in origin, and to explain certain peculiarities introduced the new conception of a portable miasm. The majority, however, sought refuge under a new cover. The class of miasmatic contagious diseases was formed, and in this amalgamated group were placed cholera, typhoid fever, yellow fever, and several other infectious diseases not conveniently classified elsewhere.

Various meanings have been and still are attached to the term miasmatic contagious diseases. Some understand by a miasmatic contagious disease one which is propagated sometimes by a contagium and sometimes by a miasm—that is, sometimes by a virus produced within the diseased body, and sometimes by a virus produced outside of the body. Others hold the opinion that for the production of cholera, typhoid fever, and other diseases of this class, two viruses or micro-organisms are necessary, one derived from a person affected with the disease, and the other derived from the soil, or at least from some external source. But the view which has gained the most adherents, and which is the prevalent one at the present time, is that a patient with typhoid fever or with cholera throws off from his body a poison, a micro-organism, which at the time of its discharge is not capable of producing the disease, but which under favorable circumstances undergoes outside of the body some unknown metamorphosis by which it acquires this power. This last view is the one which is accepted in most of the text-books on medicine published within recent years in this country and in Europe, and I presume that it embodies the belief on the subject of most practitioners of medicine.

One of my main objects in the present address is to direct your attention to what seem to me weak points in this hypothesis, and to endeavor to explain in a more natural and satisfactory manner the peculiarities of the so-called miasmatic contagious diseases, at least so far as the two leading representatives of this group, viz. cholera and typhoid fever, are concerned. The discovery of the micro-organisms which are in all probability to be regarded as the specific causes of cholera and of typhoid fever, and the investigation of their properties, should have led, it might be supposed, to a general revision of the widely accepted doctrine of miasmatic contagious diseases; but this has not been the case—at least among clinical writers, who apparently see no reason why the actually discovered germs, as well as those previously surmised, may not undergo the assumed metamorphosis outside of the body which renders them capable of infection. This is still the reasoning of Liebermeister in his work on "Infectious Diseases," published in 1885, in which he accepts the cholera and the typhoid bacilli as the agents of infection.

Let us now examine in detail the arguments which are brought forward in support of the miasmatic contagious doctrine as previously defined.

In the first place, it is urged that a metamorphosis such as is assumed to occur in the agents of infection after their elimination from the body of a cholera or a typhoid fever patient, has its analogy in the well-known instances of alternation of generation; and usually the ordinary tape-worm is cited, the ova of which, as is well known, first develop into cysticeri, and only these, when swallowed, are capable of giving rise to mature tape-worms.

The argument by analogy, however, instead of supporting the miasmatic contagious hypothesis, is directly opposed to it. In the class of organisms to which the typhoid and the cholera germs belong, no instance is known of any organism after its discharge from the body acquiring infectious properties which it did not previously possess, or of its undergoing any transformation at all resembling that assumed to occur. On the other hand, we know of some pathogenic organisms which are rendered more virulent by their passage through the body of an animal susceptible of the disease; and, in general, bacteriologists are inclined to regard as especially potent bacteria which are fresh from the bodies of infected animals. Where it is aimed to produce intoxication by means of ptomaines, as can be done by cultures of the typhoid and of the cholera bacilli, then it is

true that old cultures, as would naturally be supposed, are the most effective; but there is no reason to believe that ptomaine intoxication plays any role in the primary infection with the typhoid or the cholera germs; or, if it did, where are the ptomaines likely to be more abundant than in fresh typhoid and cholera stools?

Before we knew as much as we now do about the properties of bacteria, the transformation hypothesis now under criticism could be advanced with some show of reason; but at present our information upon this and similar points is by no means scanty, and in the absence of any pertinent analogy for such an occurrence, the assumption seems entirely unwarrantable that the specific organisms of cholera or of typhoid fever acquire new or increased virulence after their removal from the body. Inoculation experiments upon animals with the cholera bacilli lend no support to this assumption.

In the second place, it is urged in support of the miasmatic contagious theory that the specific germs of these diseases cannot be eliminated from the body in a condition capable of causing infection; otherwise those who are in proximity to the patients must frequently become infected, as in cases of small-pox or of typhus fever. This is, evidently, the argument which has the greatest weight. It is to explain the absence, or at least the infrequency of any direct communication of cholera and of typhoid fever from one person to another, that the hypothesis under consideration was constructed.

It is, of course, apparent that the specific germs of cholera and of typhoid fever must be discharged from the body in a very different way and must have very different properties from those of the contagium of small-pox and similar diseases. It is because our ideas of what characterizes a contagium are derived from our observations of such highly contagious diseases as small-pox or scarlet fever that we are loath to admit that cholera or typhoid fever patients emit anything which can be called an active contagium. I believe, also, that not a little of the difficulty of this admission comes from the popular notion that a source of active contagion must necessarily infect the surrounding atmosphere, as is the case with a small-pox patient.

It is, however, possible to reconcile the fact that the discharges of cholera and of typhoid fever patients contain a contagium, and that, too, in an active form, with the infrequency with which these diseases are communicated in a manner which is ordinarily understood as contagious.

Let us take for example cholera, and consider in the light of

recently ascertained facts what conditions must be fulfilled in order that the disease may be contracted directly from a patient. It is to be borne in mind that the cholera germ is discharged from the body only in the fæces, and very exceptionally in the vomit. It is not present in the urine, nor in the breath, nor in the sputum, nor is it thrown off from the surface of the body. These are well established facts, so that we can conclude that the only danger of direct infection from a cholera patient is by means of the stools. It is necessary, however, to come into actual contact with the stools in order to become thus infected. It has been proven by exact and very interesting experiments of Naegeli and Buchner that bacteria are never lifted by currents of air from the surface of fluids or from moist surfaces in general. One could remain in a room containing any quantity of cholera stools swarming with the cholera bacilli and there would be no danger of infection with cholera through the air. Bacteria are conveyed into the air only when they are in a dry condition, and the cholera organism is quickly destroyed by drying. So far as cholera is concerned, there is therefore no basis for the prevalent belief that the atmosphere becomes infected for a certain distance around substances containing an active contagium, although this belief is justified as regards certain other species of contagia.

But it does not suffice for infection merely to have come into contact with the cholera stools; portions of the stools must actually be swallowed. There is every reason to believe that infection with cholera takes place only through the reception of the virus directly into the alimentary canal, and not through subcutaneous inoculation or through the respiratory organs.

If this last condition be fulfilled and portions of cholera stools be actually swallowed, even then in any given case the chances are probably at least three to one that no infection would follow; for the cholera bacilli are destroyed by the acid of the gastric juice, and it is a matter of experience that only a minority of those exposed to the specific cause actually contract the disease. These considerations show how worthless are the isolated experiments of those foolhardy individuals who have voluntarily swallowed cholera dejecta and cultures of the cholera bacillus. Whatever had been the outcome of these few experiments, no positive conclusions could be drawn from them. A negative result, for reasons already given, was to be expected; a positive result would prove nothing, for the experiments were all made in districts already infected with cholera, and it would

have been impossible to decide whether infection had taken place in a natural way or as the result of the experiment. The conditions were of course entirely different in the instance of the doctor in Koch's laboratory who contracted cholera as a result of careless handling of cultures of the cholera bacilli, for there was at the time no cholera in Germany and no other possible source of infection than the cultures.

Enough has been said to show what difficulties attend the direct communication of the disease by a cholera patient. It is perfectly explicable why direct contagion is so infrequent notwithstanding the fact that cholera stools contain the contagium in an active form, indeed sometimes almost as a pure culture. There is no necessity to resort to any such artificial, complicated and unsupported hypothesis as the miasmatic contagious doctrine in the sense at present under consideration.

But any satisfactory explanation concerning the specific cause of cholera must account for occasional instances of transmission of the disease by contagion. I do not propose to discuss here in detail that most vexed question, Is cholera contagious? but I believe that he who denies absolutely the contagiousness of the disease must shut his eyes to plain facts. There are instances, and of course they are to be sought not in regions where cholera is epidemic but where sporadic cases occur, where the only natural interpretation is in favor of direct contagion.

Now the miasmatic contagious hypothesis has no room for these contagious cases, whereas there is no difficulty in accounting for occasional instances of contagion according to the view, which I believe to be an established fact, that the cholera stools contain the active cholera virus. Indeed, such instances of contagion are to be expected, although least frequently of course among doctors and nurses, whose comparative immunity is usually cited to prove the non-existence of any active contagium eliminated by a cholera patient. Doctors and nurses are the most likely to see that the cholera stools are properly disinfected, and also to disinfect their hands or other parts of their persons which may have become soiled by the dejecta. On the other hand, among ignorant persons living in cramped and unclean quarters the chances of direct contagion are much more favorable. It is probable that the statements in books relating to the frequency of cases of cholera caused by contagion are misleading, for such cases are least likely to come under the

observation of those who contribute most largely to medical literature, namely, physicians with practice in hospitals and among the well-to-do classes living under good hygienic surroundings.

There is general agreement upon the point that the epidemic spread of cholera cannot be accounted for by direct contagion. It is generally admitted that the specific agent of infection, derived from the dejecta of a cholera patient, may under favorable conditions multiply outside of the body, in the ground, upon vegetables and elsewhere. We are to seek the chief sources of infection in cholera epidemics in the drinking water, the food, the ground, in actual contact with substances containing the specific germs. A discussion of these various external sources of infection, notwithstanding the great interest and importance of the subject, is not pertinent to my present argument, which is to show not only that it is not necessary to deny the existence of an active contagium in the fresh cholera stools, but that there is every reason to believe that such contagium is actually present.

I have selected cholera for the purpose of showing the falseness of the miasmatic contagious theory as expounded by Liebermeister and others, partly because our knowledge concerning its etiology has become much more exact since Koch's discovery of its specific germ, and partly because this disease has been generally regarded as the main support of this theory. Indeed, the hypothesis of the transformation or ripening of germs after they leave the body was constructed especially to account for the phenomena of Asiatic cholera. The arguments which I have presented apply equally to typhoid fever, another important member of the miasmatic contagious group of diseases. Here, too, the specific virus is eliminated from the body, as a rule, only in the fæces. There exist the same reasons in the one as in the other disease why infection is likely to take place only exceptionally in the form of direct contagion. It is not necessary to go over the same ground with typhoid fever which we have already traversed with cholera, for as regards the points now under consideration the evidence is of the same character for both diseases.

Our information is at present wholly insufficient to enable us to form any positive opinion as to the mode of elimination of the specific virus of yellow fever.

I have attempted, gentlemen, to make it probable that a patient with cholera or with typhoid fever emits a contagium in just as active a state as a patient with small-pox or with scarlet fever. We

cannot explain the difference in frequency with which the two sets of diseases are propagated by direct contagion by assuming that only in the latter diseases is the virus eliminated in a condition capable of producing infection. The relative frequency with which infectious diseases are communicated by direct contagion depends, I believe, first of all, upon the channels through which the virus is eliminated from the body.

It may be stated as a broad proposition that every infectious disease can by artificial means be transmitted from an individual affected with the disease to another individual susceptible of the disease. This is only the natural inference from the fact that each infectious disease has its specific virus in the shape of a micro-organism which is present and multiplies in the bodies of those affected with the disease. Although there is no evidence that under natural conditions malaria is ever transmitted from one person to another, still it is possible to accomplish this artificially, as has been proven by the experiments of such trustworthy observers as Gerhardt and Marchiafava and Celli, who inoculated successfully, with blood from malarious patients, persons who were entirely free from malaria.

Strictly speaking, therefore, in every infectious disease there is a contagium, but we should fall into grave errors if we drew our conclusions as to the natural modes of infection from the results of artificial inoculations, as is illustrated by the example of malaria.

To explain why, under natural conditions, some diseases, such as the exanthematous fevers, are usually transmitted by contagion; other diseases, such as typhoid fever and cholera, only infrequently, and other diseases, such as malaria, never by contagion, it is necessary, I repeat, to consider the channels by which the virus is eliminated, if at all, from the body.

If, as in the case of malaria, the virus is not discharged at all from the body, then of course there is no possibility, under the conditions of nature, of the communication of the disease from one person to another. If, as in the case of cholera and of typhoid fever, the virus is discharged only by way of the fæces, then contagion is possible, but it is not likely to occur with ordinary care and with ordinary cleanliness. If, as in the case of scarlet fever, measles and small-pox, the virus is eliminated from the skin and adheres to thin scales of epidermis which can be readily transported through the air, then contagion is likely to be a common occurrence.

I do not wish to be understood as implying that the mode of

elimination of a virus is the sole factor in determining the degree of contagion of a disease. There are, of course, other important factors, such as the degree of resistance offered by the virus to drying, the chances of its being conveyed into the air, its quantity, etc., as well as the degree of susceptibility which exists on the part of those exposed and the portal through which the virus must enter in order to cause infection.

I trust, gentlemen, that this will be found a more rational, fruitful and satisfactory way of regarding the infectious diseases than to wander among the mazes of miasmatic, contagious, and miasmatic contagious diseases, and to imagine that in some diseases the virus is eliminated in a potent state, and in other diseases in a state requiring some subsequent transformation to make it potent.

It is unfortunate that our positive knowledge concerning the mode of elimination from the body of the specific poisons of the various infectious diseases is still very incomplete. Only for those diseases whose special agents of infection have been discovered is our information exact upon this point. For some other diseases we have good grounds for forming an opinion, while in the case of several infectious diseases, such as relapsing fever, we are quite in the dark on the subject.

It may not be out of place to call your attention to certain points which bear upon this question. The experiments of Wyssokowitsch, made in the Hygienic Laboratory of Göttingen, and published not quite a year ago, have shown that non-pathogenic bacteria injected into the blood of animals in a few hours disappear from the blood and are deposited in certain organs, especially the liver, the spleen, and the marrow of the bones, whence they also disappear, as a rule, in a short time. They are not eliminated by the urine or by any other excretion. He found that micro-organisms in general are discharged by the urine only when they form some local lesion in the kidney or some part of the urinary tract. He found, likewise, that organisms injected into the blood are not discharged by the intestine unless they first cause some lesion of the alimentary canal. Similar facts were determined regarding secretions from other mucous membranes. The experiments of Wyssokowitsch warrant the following statements:

The specific germs of infectious diseases can be and, in cases of recovery, doubtless often are, destroyed within the body.

Contrary to what many have believed, the kidneys and the intes-

tines cannot be regarded as important means of freeing the body from micro-organisms which have gained access to the blood.

When the specific micro-organisms of an infectious disease are found in the urine or in the fæces, it may be inferred that the genito-urinary apparatus and the alimentary tract respectively are the seat of some lesion produced by these organisms.

These experiments justify also the inference, in itself probable enough, that the specific viruses of infectious diseases are discharged from those free surfaces which are themselves the seats of the characteristic lesions of the disease, as for instance from the respiratory tract in pulmonary tuberculosis, lobar pneumonia, whooping cough, diphtheria; from the skin, in scarlet fever, measles, small-pox, typhus fever, erysipelas; from the intestines, in typhoid fever, cholera; from the urethra or vagina in gonorrhœa, syphilis. For several diseases, however, we have no satisfactory data for determining in what manner the special poison is eliminated. This is true, for instance, of cerebro-spinal fever and relapsing fever.

We are ignorant as to whether micro-organisms may be eliminated by the breath, although it is a common notion that this occurs. In view of the experiments already cited, which show the difficulty with which micro-organisms are detached from moist surfaces by currents of air, it seems improbable that organisms can be conveyed from the body by the breath. Of course, if the organisms were momentarily set free by acts of coughing, then they might be carried on by the respiratory current, but it is at least very questionable whether in ordinary breathing particulate substances can be thus transmitted.

We have up to this point, gentlemen, considered only the diseased body and its fresh excreta as the source of infection, and we have reached the conclusion that in every infectious disease there is a contagium, but that whether or not the disease is likely to be propagated as a contagious one depends upon various circumstances, among which the mode of elimination of the contagium from the body is of the utmost importance.

A question of great interest, as well as of practical importance, is whether or not any given infectious agent finds conditions outside of the body favorable for its prolonged existence. This question is not identical with that of the reproduction of the special virus outside of the body. The importance of the latter point has been somewhat exaggerated in discussions relating to the etiology of infectious diseases. Special agents of infection may be widely distributed

without their finding conditions favorable to reproduction outside of the animal body. Thus the bacillus of tuberculosis appears to be almost as widely spread throughout nature as the organisms which cause suppuration, and yet the tubercle bacillus can find only exceptionally the conditions of temperature and of nutriment which permit its multiplication outside of the body, whereas the pus organisms doubtless find abundant opportunities for their development on various substances outside of the body.

The mere facts of the wide distribution of certain infectious micro-organisms and of frequent infection from external sources do not justify us in drawing conclusions as to the capability of growth of the organisms as saprophytes. This is a point which can be positively decided only by a knowledge of the life history and properties of the different infectious organisms.

So far as our present knowledge reaches, it is only such infectious micro-organisms as form spores which are capable, under natural conditions, of prolonged existence outside of the body without reproduction. These spores can resist high temperatures, drying, and various other agencies which are destructive to the ordinary vegetative cells. Thus we can explain why, for instance, infection with the tubercle bacillus can take place from external sources, while infection with gonorrhœa always requires contact with fresh gonorrhœal secretion, although in neither instance does the special virus reproduce itself outside of the animal body, except under such artificial conditions as we can produce in our laboratories.

The question as to the reproduction of infectious micro-organisms outside of the body, although it has not all of the significance sometimes attached to it, is nevertheless one of much interest. It is from this point of view that infectious micro-organisms are often classified by bacteriologists. Thus there are micro-organisms which find only within the animal body the conditions suitable for their growth and development. Such organisms are called obligatory parasites. Examples are the parasitic organisms of syphilis, gonorrhœa, tuberculosis, and doubtless of small-pox, measles, scarlet fever, etc. Other infectious micro-organisms are capable of growing under natural conditions both within the body and outside of the body, as in the soil. Such infectious agents are called by bacteriologists potential parasites. In the case of some of the potential parasites their natural home seems to be the animal body, as appears to be true, at least in most localities, of cholera and typhoid fever bacilli; while in other

cases the natural habitat of the organism is the soil, whence it makes occasional excursions into the animal body. The malarial parasite conforms to the latter type. The growth of micro-organisms outside of the body is spoken of as saprophytic.

In the case of typhoid fever there is no *a priori* objection to supposing that its parasite may grow in situations where it has not been introduced by any human being. The weight of evidence seems certainly opposed to such a supposition; still Murchison and other authorities have contended for the so-called spontaneous origin of typhoid fever in some cases, and the question can be settled only by a careful analysis of epidemiological facts, in the interpretation of which there inhere, as is well known, important sources of error.

Of the utmost importance in the elucidation of the spread of many of the infectious diseases, particularly of cholera and of typhoid fever, is the investigation of the conditions favorable to the existence and growth of parasitic micro-organisms in the soil, the drinking water, upon vegetables and other substances outside of the body, as well as of the means by which infection occurs from these external sources. These subjects, which pertain to public hygiene, can be touched upon only very briefly upon this occasion.

More attention has been paid to the influence of the soil and of the drinking water in the propagation of epidemic diseases than to any other of the factors named. Under the brilliant leadership of Pettenkofer a school of hygienists has developed who lay emphasis almost exclusively upon the soil in this matter, and are unwilling to admit that epidemic infection takes place through the drinking water.

We owe to this school valuable researches as to the physical conditions of the soil which favor the development into an epidemic of such diseases as cholera and typhoid fever, as well as to conditions hostile to such development. Among the conditions favorable to an epidemic may be mentioned a certain degree of porosity of the soil, a certain amount of moisture, and some impregnation with decomposing animal and vegetable material. But notwithstanding these painstaking investigations, which are much more extensive than this brief notice would indicate, it must be admitted that they have left us considerably in the dark as to how we are to regard the soil as concerned in the propagation of infectious diseases. There has been no actual demonstration of the infectious micro-organisms of cholera and of typhoid fever in the soil, or of their multiplication there,

and, above all, no satisfactory explanation as to the means by which infectious agents are transported from the soil to the animal body.

To the medical profession in this country and in England it is not comprehensible how there can still be distinguished authorities who deny that epidemics of typhoid fever or of cholera are ever attributable to the drinking water. Yet in Germany there are hygienists who are not only quite positively, but even somewhat violently opposed to what they call the drinking water hypothesis. It is doubtless true that we are often too ready to accuse the drinking water in an outbreak of typhoid fever; but if medical evidence is worth anything, there can be no reasonable doubt that many epidemics of typhoid fever have been due to contamination of the drinking water with the typhoid virus.

The experiments of Meade Bolton have revealed the important fact that most pathogenic micro-organisms do not multiply in water sufficiently pure ever to be used for drinking purposes. Not only do the pathogenic bacteria not multiply in drinking water, but, if they do not contain spores, most of them are destroyed in drinking water in a short time, varying from a few hours to several days, according to the species and the quantity of bacteria. These experiments have been hailed by the Munich school of hygienists as opposed to the view that epidemic infection can take place through the drinking water, but they need not be so interpreted, nor are they so interpreted by Bolton.

These experiments make it necessary to suppose that a single infection of the drinking water with infectious organisms would not suffice for an epidemic lasting more than a few days. To keep up a long-continued epidemic by means of contaminated drinking water, there must be some communication between the water and some focus in which the disease-producing organisms are present in large number or are multiplying. This is in harmony with the fact that repeatedly in epidemics traceable to the water, communications have been proven to exist between the water and cess-pools, drains, privies, or other possible foci of infection. In considering water as a source of infection, one must remember that this can occur not only by drinking, but also by the use of the water in cooking, and in washing dishes subsequently used to contain food.

As is well known, there have been several epidemics of typhoid fever in which the source of infection has been traced to the milk. Although in these instances it was believed that the milk was itself

infected by the addition of contaminated water, nevertheless it is well to note that in one important particular milk differs from water in its behavior toward pathogenic micro-organisms. Milk is an excellent nutritive medium for nearly all of these organisms. The typhoid and the cholera bacilli grow in milk rapidly and abundantly, without producing any alteration in the external appearance of the milk. Inasmuch as certainty of infection depends, in the case of many diseases, upon the number of organisms which enter the body, it is apparent that this property imparts a particularly dangerous character to infected milk.

As regards the means of transportation by which the agents of infection are conveyed from external objects to the body, the most important is believed to be the air by those who lay the most stress upon the influence of the soil in the spread of epidemic diseases. It seems probable, however, that too big a role has hitherto been assigned to the air as a carrier of contagion. The fact has already been mentioned that currents of air are incapable of lifting bacteria from moist surfaces; and Naegeli has shown, also, that if bacteria be dried with their natural gelatinous envelopes or from albuminous substances, they are in much the same physical condition as insects attached to a surface by mucilage, and cannot be carried away by the air unless they are first converted into a dust-like powder. If it be furthermore considered that some bacteria are destroyed by complete desiccation, it is evident that these facts compel us to restrict within much narrower limits than most writers have done, the importance of the air in the transportation of agents of infection. Still there remains evidence enough that the virus of some diseases, notably of malaria, and probably of yellow fever, may be, and often is, conveyed through the atmosphere. As infection through the air is something which we have no means of combating, it is encouraging to learn that this resistless fate has a narrower sway than we had been led to believe.

There are many grounds for supposing that the chief means of infection are by actual contact, in one way or another, with the agents of infection. The conviction of the truth of this statement is borne in almost irresistibly upon one who has engaged extensively in the cultivation of micro-organisms. I have kept for weeks at a time, side by side in a sterilized dish to which filtered air had free access, two watch-glasses, one containing a culture of the typhoid bacilli in beef tea, the other containing simply sterilized beef tea. During

this time, notwithstanding its close proximity to the typhoid culture, the beef tea in the second glass remained perfectly pure, without a trace of contamination from its neighbor. Many illustrations of the same principle might be drawn from the work of a bacteriological laboratory. We study the exposed cultures of such pathogenic organisms as the anthrax bacilli, the cholera bacilli, the glanders bacilli, and run no risk of infection from these so long as we do not come into contact with the cultures.

There is one observation which we sometimes make in our laboratories in summer—to our discomfiture—which, although it may seem trivial, is not without its practical bearings. This is the readiness with which micro-organisms may be disseminated by flies and other insects. Upon the so-called plate cultures we can sometimes trace the devious wanderings of an insect by the colonies of micro-organisms which it has planted in its course. The application of this experience to a possible means of transportation of the special organisms of infectious disease is too apparent to need further elucidation.

I shall not weary you by attempting to elaborate in all of its details the doctrine that one of the chief means of infection is by contact. There are thousands of ways in which we can inadvertently come into contact with sources of infection. This teaches us that it is an error to construct exclusive theories of infection, such as are expressed by the terms "soil hypothesis," "drinking water hypothesis," etc.

There is one lesson, however, which has come from the epidemiological study of the relations of the soil and of the drinking water to infectious diseases, and that is the immense importance of the proper disposal of the refuse matter around human habitations and the supply of pure drinking water. The efficacy of a good system of drainage or of sewerage in preventing the development of many epidemic diseases is probably to be sought, not in the purifying of the ground so that pathogenic organisms cannot grow there, but in affording means by which these organisms, contained in human excreta and other substances, are readily carried away. The discussion of these points relates to sanitary science, and does not belong to my theme, but I cannot refrain from a brief allusion to the subject on account of its great practical importance.

What can be more instructive, as well as more encouraging, than to witness the manner in which Asiatic cholera, during its present

journey, has failed to secure any foothold in those European cities which are characterized by cleanliness and proper sanitary arrangements, although it has been repeatedly introduced into such cities? These cities have secured their immunity, not by spasmodic precautionary efforts after the entrance of the disease, but at the price of systematic, vigilant and intelligent exertions during what may be termed the time of peace. Without wishing to pose as an alarmist, I believe that with the announcement of the appearance of Asiatic cholera upon this continent, the time has come to emphasize the fact that the only enlightened and civilized public policy is to be prepared at all times and in all places to meet the enemy.

Of the various factors entering into the causation of infectious diseases none is more obscure than that designated predisposition, and yet this is a factor with which we must undoubtedly reckon. This mysterious predisposition to certain infectious diseases plays, perhaps, even a greater role with us, at the present time, than it did with our forefathers in medicine, who wrote so much concerning *constitutio epidemica.*

It cannot be said that the increase in our knowledge concerning the specific causes of infectious diseases has illuminated to any great extent what is meant by predisposition, and still a few glimmers of light have been sent into this dark corner by recent bacteriological investigations.

Mention has already been made of the fact that the cholera bacilli are destroyed by the acid gastric juice, so that we are warranted in regarding all conditions which neutralize the acidity of the gastric juice as affording predisposition to this disease.

Perhaps the most positive addition to our knowledge in this direction has been the demonstration of the importance of pre-existing diseases or lesions of structure in affording ready means of ingress and suitable conditions for the lodgment and growth of pathogenic micro-organisms within the body. In this connection attention may be called to the experiments of Wyssokowitsch and of Prudden, which show the necessity of previous alterations of structure in the cardiac valves before they are adapted for the lodgment and development of the micro-organisms which cause ulcerative endocarditis. Grawitz has shown that the bacteria of suppuration may be injected in large quantity into the healthy peritoneal cavity without doing any damage, but that they set up suppurative peritonitis if they meet there wounded tissues, stagnating fluids, or so-called dead spaces from which they are not readily absorbed.

Especially instructive in this light is the study of the manifold complications which attend scarlet fever, typhoid fever, and other diseases which are accompanied by necroses and ulcerations of the mucous membranes of the throat, intestine, and other parts with which micro-organisms are normally in contact. While it has been shown that most of these micro-organisms are harmless, there are not infrequently among them some which are pathogenic, such as the cosmopolitan bacteria of suppuration. The superficial necroses and ulcerations of the mucous membranes in scarlet fever and typhoid fever afford means of ingress for these bacteria, which often find within the body foci of least resistance resulting from the existing diseases. We are therefore not surprised to learn that many of the complications of these diseases are produced by the staphylococci and streptococci of suppuration, or that there are frequently found in these diseases in the tissues and fluids bacteria, particularly micrococci, which have nothing to do with the specific cause of the primary disease, although often enough mistaken for it by hasty observers.

Time will not permit me to elaborate the ideas here touched upon. Enough has been said to show that we need not despair of gaining some definite conception as to the nature of predisposition and immunity to disease, but we must not forget that our positive knowledge at present touches only the outlying boundaries of the subject. We do not even know why different species of animals behave differently toward infectious agents—why, for instance, house mice resist the deadly glanders bacilli, while the more hardy field mice readily succumb—still less can we account for differences in susceptibility of individuals of the same species.

It is easy enough to construct plausible theories of predisposition and of immunity, and such theories have their scientific uses; but we must remember that we have gained no explanation of the facts when we base our theories upon such popular phrases as struggle for existence between cells and bacteria, or fitness of the soil for the growth of bacteria, etc. Even the more tangible phagocytic doctrine of Metschnikoff cannot be said to have materially advanced our knowledge as yet, or to have met with much support in facts.

Before leaving this subject it may be well to say that possibly we are at present in the habit of assigning too great importance to predisposition as a factor in the causation of infectious diseases. It is such a convenient refuge that we are tempted to bury in its obscurity many etiological facts which we cannot readily explain.

While I would not by any means ignore the importance of hereditary predisposition to tuberculosis, is it not probable that cases are often included in this category which do not belong there? When we think of the especial dangers of infection to which the offspring of tuberculous parents are exposed from their youth upward, of the likelihood that a child will follow an occupation which has favored the development of phthisis in a parent, and of the frequency with which the concurrence of the disease in ancestor and descendant is mere coincidence, it is apparent that we are in danger of assigning to heredity a larger part in the causation of tuberculosis than it deserves.

It must be admitted that the instances in which we have been able by experiments upon animals of the same species to demonstrate different degrees of predisposition toward infectious agents are not very striking or very numerous.

And now, gentlemen, I bring to conclusion this imperfect survey of some points relating to the etiology of infectious diseases. We are only upon the threshold of a deeper insight into the nature of a class of diseases which have been more devastating to the human race than any upheavals of nature or any wars. They have left their imprint upon the political, the social and the intellectual history of the world. One need not be of a very sanguine temperament to hope that our steadily increasing knowledge will bear fruit, not only, as in the past, in the prevention of these diseases, but also in a rational system of causal therapeutics.